National High Blood Pressure Education Program (NHBPEP)

# *Working Group Report on* High Blood Pressure in Pregnancy

MH88D0904

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

National Institutes of Health

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NIH Publication No. 90-3029

August 1990

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# Executive Summary

High blood pressure complicates almost 10 percent of all pregnancies, and the incidence is higher if the women are nulliparous or carrying multiple fetuses. Causes of hypertension in pregnancy are multiple, and many current and previously used classification systems are elaborate and confusing, due in part to difficulty in making an etiological diagnosis by clinical criteria alone. The consensus group recommends the schema proposed by the American College of Obstetrics and Gynecologists in 1972, which has been in wide use for some time, is practical and concise, and considers hypertension associated with gestation in only four categories: I. chronic hypertension (of whatever cause, but mainly essential in nature); II. preeclampsia; III. preeclampsia superimposed upon chronic hypertension; and IV. transient hypertension.

Preeclampsia (pure or superimposed) represents the greatest danger for the fetus and is associated with life-threatening maternal syndromes, while transient hypertension is a fairly benign disorder characterized by mild to moderate elevations of blood pressure late in pregnancy which return to normal postpartum. Essential hypertension, too, is usually well tolerated if elevations remain (with or without therapy) below diastolic* levels of 100 mm Hg (phase V), but complications such as midtrimester loss, growth retardation, and abruption may occur more frequently. Because the preeclamptic syndromes and essential hypertension comprise over three-quarters of the hypertensive disorders in pregnancy, this document focuses on the presentation, pathophysiology, and management of these diseases.

Preeclampsia, a disease peculiar to pregnancy, mainly in nulliparas, presents primarily after gestational week 20, most frequently near term. Signs helpful in its diagnosis are presence of proteinuria, edema (especially if of recent and rapid onset), and any of the following: hemoconcentration, hypoalbuminemia, hepatic function and/or coagulation abnormalities, and increased urate levels. The predictive value of raised serum iron, low antithrombin III, and hypocalciuria are under investigation.

A major pathophysiological feature of this disease is a marked increase in peripheral resistance. This vasospasm is due, in part, to exaggerated vascular responsiveness to circulating angiotensin II and catecholamines (and possibly an imbalance between thromboxane and prostacyclin production). Prior to intervention, cardiac output is often decreased, pulmonary capillary wedge pressure is normal or low, and intravascular volume is below that of normal pregnant women. Renal hemodynamics also decrease due, in part, to a characteristic morphological lesion in the glomerulus, and there may be increased vascular permeability leading to albumin loss from the intravascular space. Uteroplacental perfusion is often compromised, which may lead to fetal growth retardation.

Preeclampsia can lead to two life-threatening complications. The first is a rapidly developing syndrome characterized by microangiopathic hemolytic anemia and marked signs of liver dysfunction as well as coagulation changes. This variant, termed HELLP

* Diastolic blood pressure, in this document, is defined as the onset of Korotkoff phase V (disappearance of sound).

(hemolysis elevated liver enzymes low platelet count), constitutes an emergency requiring prompt pregnancy termination. The second complication is progression of preeclampsia to a convulsive phase termed eclampsia, at one time the major cause of cerebral bleeding and maternal mortality in this disorder. Pending or frank eclampsia also requires immediate termination of gestation.

Therapy for preeclampsia when gestation is advanced is delivery. Severe intrapartum hypertension is controlled with intravenous hydralazine, which is successful in most instances. Favorable results have been recorded with parenteral diazoxide, labetalol, and clonidine as well as oral nifedipine. Nitroprusside should be avoided unless maternal jeopardy is extreme. Magnesium sulfate remains the drug of choice to prevent or treat eclamptic convulsions.

Women with essential hypertension often experience reductions in blood pressure during the first two trimesters; failure for this to occur is an unfavorable prognostic sign. When pharmacological intervention is required, alpha methyldopa, because of its long history of safe use and a trial including a 7-year followup of the neonate, remains the drug of choice to treat chronic hypertension in pregnancy. Data relevant to beta blocking agents and combined beta and alpha adrenergic receptor antagonists demonstrate their usefulness with little or no evidence of fetal jeopardy. Thiazide diuretics, which have been used safely in normotensive gravidas, may be used in hypertensive pregnant women—especially those who are salt sensitive. Preliminary information concerning calcium channel antagonists is also encouraging, but angiotensin converting enzyme inhibitors are contraindicated in pregnant women.

Finally, like all pregnant women, those with hypertension should refrain from alcohol and tobacco. The roles of calcium supplementation and low-dose aspirin (which decreases thromboxane synthesis while sparing prostacyclin production) to prevent preeclampsia and/or chronic and transient hypertension are under investigation.

# Introduction

The hypertensive disorders during pregnancy are important causes of maternal death throughout the world, and most of these deaths are attributed to eclampsia. The hypertensive disorders also extensively contribute to stillbirths and neonatal morbidity and mortality. Hypertensive expectant mothers (or gravidas) are predisposed to the development of potentially lethal complications, notably abruptio placentae, disseminated intravascular coagulation (DIC), cerebral hemorrhage, hepatic failure, and acute renal failure.

The prevalence of chronic hypertension in pregnancy (that is, in those hypertensive women who become pregnant) is not known. It differs widely in different geographic areas but is probably present in 1 to 5 percent of all pregnancies.[1] The number of women who become hypertensive during pregnancy (preeclamptic) is also unclear, but one estimate from an indigent population is calculated to be about 13 percent,[2] and incidences ranging from 10 to 20 percent have been noted in nulliparous women.[3-6]

The purpose of this report is to provide guidance to the practicing physician in 1) managing hypertensive patients who become pregnant (hypertension that is present and observable prior to pregnancy or diagnosed before the 20th week of gestation) and 2) managing pregnant patients who become hypertensive (the pregnancy-specific condition termed preeclampsia). This report expands on the recommendations of *The 1988 Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure* (JNC IV).[7]

# Classification of Hypertensive Disorders of Pregnancy

The most important consideration in the classification of increased blood pressure during pregnancy is the differentiation of hypertension that antedates pregnancy from a pregnancy-specific condition, which is characterized by poor perfusion of many organs and which usually has increased blood pressure as one of its features. In the former condition, elevated blood pressure is the cardinal pathophysiological feature, while in the latter, increased blood pressure is important primarily as a sign of the underlying disorder. As might be expected, the impact of these two conditions on mother and fetus is quite different, as is their management. Unfortunately, attempts to differentiate these two classes of patients have led to confusion in terminology worldwide. The system proposed by the American College of Obstetricians and Gynecologists (ACOG) in 1972,[8] although imperfect, has been in wide use for some time and has the advantage of clarity and simplicity.* Using this terminology, women with increased blood pressure are divided into the following groups:

- Chronic hypertension
- Preeclampsia-eclampsia
- Preeclampsia superimposed upon chronic hypertension
- Transient hypertension.

* More recent classifications are available from the ACOG,[9] World Health Organization,[10] and the International Society for the Study of Hypertension.[11] This working group elected to use the earlier classification for purposes of clarity.

## Chronic Hypertension

Chronic hypertension is defined as hypertension that is present and observable prior to pregnancy, or that is diagnosed before the 20th week of gestation. Hypertension is defined as a blood pressure equal to or greater than 140/90 mm Hg. Hypertension that is diagnosed for the first time during pregnancy and that persists beyond the 42nd day postpartum is also classified as chronic hypertension.

## Preeclampsia-Eclampsia

The pregnancy-specific condition is termed preeclampsia in the ACOG classification[8] and usually occurs after 20 weeks gestation (or earlier with trophoblastic diseases such as hydatidiform mole or hydrops). It is determined by increased blood pressure accompanied by proteinuria, edema, or both. Either of the following criteria suffice for the diagnosis of hypertension in this situation: 1) systolic blood pressure increases of 30 mm Hg or greater or 2) diastolic blood pressure increases of 15 mm Hg or greater from early values (average of values prior to 20 weeks gestation). If prior blood pressure is not known, readings of ≥140/90 mm Hg after 20 weeks gestation are considered sufficiently elevated to satisfy the blood pressure criteria of preeclampsia. Note, however, that many young pregnant women will show the blood pressure increase required for the diagnosis of preeclampsia without increasing their pressure to 140/90 mm Hg.

In preeclampsia and eclampsia, the blood pressure often is widely variable from moment to moment, and two observers

measuring the blood pressure successively may obtain very different readings.

Proteinuria is defined as the excretion of 0.3 gm or greater in a 24-hour specimen. This will usually correlate with 30 mg/dL ("1+ dipstick") or greater in a random urine determination. Proteinuria usually is a late sign in the course of preeclampsia; although it is nonspecific, its appearance greatly bolsters the diagnosis of preeclampsia. Edema is diagnosed as clinically evident swelling, but fluid retention may also be manifested as a rapid increase of weight without evident swelling.

Preeclampsia always presents potential danger to mother and baby. However, certain signs are particularly ominous:

- Blood pressure of 160 mm Hg or more systolic, or 110 mm Hg or more diastolic.
- Proteinuria of 2.0 gm or more in 24 hours (2+ or 3+ on qualitative examination). *The proteinuria should occur for the first time in pregnancy and regress after delivery.*
- Increased serum creatinine (>1.2 mg/dL unless known to be previously elevated).
- Platelet count <100,000 μL and/or evidence of microangiopathic hemolytic anemia (with increased lactic acid dehydrogenase).
- Elevated hepatic enzymes (ALT or AST).
- Headache or other cerebral or visual disturbances.
- Epigastric pain.
- Retinal hemorrhage, exudates, or papill-edema. *These are extremely rare. It is most unlikely that they would occur in the absence of other major signs of severe disease. When present, these signs almost always denote underlying chronic hypertension.*
- Pulmonary edema.

Eclampsia is the occurrence of seizures, in a preeclamptic patient, that cannot be attributed to other causes.

## Preeclampsia Superimposed Upon Chronic Hypertension

There is ample evidence that preeclampsia may occur in women already hypertensive (i.e., who have chronic hypertension) and that the prognosis for mother and fetus is much worse than with either condition alone. The Committee on Terminology[8] recommended that the diagnosis be made on the basis of increases of blood pressure (30 mm Hg systolic or 15 mm Hg diastolic, or 20 mm Hg mean arterial pressure) together with the appearance of proteinuria or generalized edema.

## Transient Hypertension

Transient hypertension is the development of elevated blood pressure during pregnancy or in the first 24 hours postpartum without other signs of preeclampsia or preexisting hypertension. This condition is often predictive of the eventual development of essential hypertension. This is obviously a retrospective diagnosis, and if any uncertainty regarding the diagnosis exists, these patients should be managed as preeclamptics.

## Problems With Classification

Problems are inherent in the use of blood pressures measured in early pregnancy to diagnose chronic hypertension or to define basal blood pressure for the diagnosis of preeclampsia. Blood pressure usually decreases early in pregnancy, reaching its nadir at about the stage of pregnancy at which women usually seek obstetrical care. The decrease averages 7 to 10 mm Hg for diastolic readings. In some women, obviously, blood pressure decreases more than 7 to 10 mm Hg, and the early decline and subsequent return of blood pressure to or toward prepregnant levels in late gestation will be sufficient to diagnose preeclampsia. Since women who are hypertensive prior to pregnancy have a greater decrease in blood

pressure in early pregnancy than do normotensive women,[12] they are even more likely to be erroneously diagnosed as preeclamptic according to blood pressure criteria.

It is well established that seizures due to eclampsia may occur when the blood pressure is only mildly increased.[13,14] Therefore, any rise in blood pressure in a pregnant woman is potentially dangerous, and the final diagnosis of "mild" or "severe" preeclampsia should not be made until after the patient delivers and returns home.

Even the triad of proteinuria, edema, and hypertension is nonspecific; each sign could be due to conditions other than preeclampsia. Edema is a physiologic finding present in many normal pregnant women. There is no reason to believe that the normal physiologic edema of pregnancy should not occur in women with transient hypertension, but when it does, the clinically oriented classification calls for the diagnosis of preeclampsia (almost always "mild preeclampsia"). Transient hypertension is sometimes the preproteinuric phase of preeclampsia and sometimes the recurrence of chronic hypertension abated in midpregnancy, but more often it seems to be a manifestation of latent essential hypertension brought to light by pregnancy, as several followup studies have shown.[15-17] Transient hypertension has a high rate of recurrence in later pregnancies (up to 88 percent) and probably is the usual basis for the erroneous diagnosis of preeclampsia in multiparas.

The diagnosis of superimposed preeclampsia is especially difficult. Women fulfilling diagnostic criteria for superimposed preeclampsia may indeed have preeclampsia, but in some of these women the origin of signs may instead be renal disease, either causing the hypertension or secondary to it, that may coincidentally worsen during pregnancy. Conversely, many women who actually develop preeclampsia may not have the condition diagnosed. This is a special problem in women receiving antihypertensive therapy, in whom early stages of superimposed preeclampsia without proteinuria may be masked by therapeutic lowering of blood pressure. Superimposed preeclampsia is especially difficult to diagnose in the hypertensive woman with proteinuria at the onset of pregnancy. To aid in diagnosis, investigators have suggested using criteria such as increasing levels of serum uric acid and decreasing platelet counts.[18]

Preeclampsia has a clinical spectrum ranging from mild to severe forms and then potentially to eclampsia. Affected patients do not "catch" eclampsia but progress through this spectrum. In most cases, progression will be slow and the disorder may never proceed beyond mild preeclampsia. In others, the disease may progress more rapidly, changing from mild to severe over days to weeks. In the most serious cases, progression may be fulminant, with mild preeclampsia evolving to severe preeclampsia or eclampsia within days or even hours. *Thus, for clinical management, preeclampsia should be overdiagnosed, because a major goal in managing preeclampsia is the prevention of eclampsia, primarily through timing of delivery.*

More stringent criteria must be used in the selection of cases for research studies of preeclampsia. No classification is accurate or verifiable in the absence of a good understanding of the cause of preeclampsia to permit the development of a specific diagnostic test. Definitions that depend on a numeric threshold arbitrarily imposed on a continuous spectrum of changes (e.g., rising blood pressure) create artifacts around the chosen threshold. This is particularly true of the definitions for hypertension in pregnancy and preeclampsia. A major obstacle to the advancement of our knowledge of preeclampsia-eclampsia is the publication of studies of "mild preeclampsia" because the diagnosis is likely to be erroneous in half the cases; the women may have preeclampsia, transient hypertension, or chronic hypertension that abated during much of pregnancy, or any of a wide variety of renal diseases.[19]

Another problem pertinent to clinical management is that some women with pregnancy-specific pathophysiologic changes identical to those present in preeclampsia—including coagulation and liver function abnormalities—will not have the specific signs of preeclampsia sufficient to satisfy the ACOG definition.[20] These women are nonetheless at increased risk, as are their infants, and should be managed like the more typical preeclamptic patient.

In spite of the difficulties in making the clinical diagnosis, there is no question that a pregnancy-specific condition (preeclampsia in the ACOG committee's classification)[8] —in which reduced perfusion to many organs including the placenta—results in increased maternal and fetal morbidity and mortality. Unlike chronic hypertension, in which hypertension is the important pathogenic factor, in preeclampsia blood pressure is usually important primarily as a marker of disease. Also unlike chronic hypertension, which slowly progresses over years, preeclampsia can proceed rapidly, with attendant increased risk to mother and baby. Thus, it is mandatory to attempt to differentiate these disorders in order to appropriately manage the pregnant woman with increased blood pressure. *If a diagnosis of preeclampsia cannot be excluded, it is most appropriate to manage the woman as preeclamptic.*

# Blood Pressure in Normal Pregnancy and the Epidemiology of Hypertensive Disorders

As previously noted, diastolic pressure decreases by an average of about 7 to 10 mm Hg early in gestation, with a rise to or toward the (assumed) prepregnancy level in the third trimester. Only minimal changes in the systolic pressure seem to occur, which is reasonable because the increase of 30 percent to 40 percent in the cardiac output largely offsets the decrease in total peripheral resistance.

The following factors predispose to preeclampsia-eclampsia:

- Primigravidas are from six to eight times more susceptible than are multiparas.[21]
- About one-third of primigravidas who have had eclampsia develop hypertension in about 20 percent of later pregnancies, but generally they have mere rises in blood pressure alone (transient hypertension) rather than preeclampsia. Only 10 to 15 percent have proteinuric hypertension.[1] Transient hypertension, usually miscalled mild preeclampsia in the past as well as in some current classifications, recurs in 80 percent[16] to 88 percent[15] of women pregnant again and often portends ultimate chronic hypertension.
- Women who have had preeclampsia or eclampsia as multiparas usually have some predisposing factor, often chronic hypertension; in these women the recurrence of superimposed preeclampsia may be as high as 70 percent.[1]
- The tendency for preeclampsia is inherited.[22]
- Twin pregnancy increases the risk five times.[21]
- Diabetes is a potent factor, but relative risk cannot be specified because diabetics often have other forms of hypertension that confuse the diagnosis.[23]
- Large, rapidly growing hydatidiform moles increase the risk 10 times in both primigravidas and multiparas.[24]
- Fetal hydrops increases the risk 10 times in both primigravidas and multiparas.[25]

Relative risk of chronic hypertension cannot be estimated because the incidence of superimposed preeclampsia varies greatly—as diagnosed and greatly overdiagnosed—from one center to another.

Contrary to popular belief, hydramnios alone[26] and social class[27] do not predispose to preeclampsia, which has the same incidence in white and black American women. Lack of prenatal care may lead to failure to recognize this condition in its early stages. Black women in the childbearing age have two to three times the prevalence of essential hypertension than white women. In blacks, frank and latent chronic hypertension and transient hypertension often are misdiagnosed as preeclampsia.

Pregnancy can be considered a screening test for ultimate chronic hypertension because women having normotensive pregnancies, especially after age 25, have a low likelihood of developing later chronic hypertension; women with transient hypertension have a high probability of ultimate essential hypertension. Preeclamptic and eclamptic hypertension predict nothing, because the disorder does not permit the screening. Had it not been for the intercurrent and unrelated preeclampsia, the pregnancy could have been either normotensive or complicated by transient hypertension.

# The Pathology and Pathophysiology of Hypertension in Pregnancy Focusing on Preeclampsia

## Vasospasm

Vasospasm is presumed basic to the pathophysiology of preeclampsia-eclampsia. Vascular constriction causes resistance to blood flow and subsequent arterial hypertension. In some presentations the cardiac output is not maintained, and the resulting absent or mild hypertension underestimates the severity of the disorder. In this context it should be noted that there is good evidence for the condition of "normotensive preeclampsia."[28] Vasospasm and associated vascular damage which cause endothelial cell leaks, together with local hypoxia of surrounding tissues, presumably lead to hemorrhage, necrosis, and other end-organ disturbances of severe preeclampsia.

Vascular reactivity to infused angiotensin II and catecholamines is decreased in normal pregnancy. There is an increased pressor response to some vasoactive hormones in early preeclampsia,[29] and this increased response clearly precedes the onset of hypertension.[30] Angiotensin II refractoriness, observed in normal pregnancy, may be mediated by vascular endothelial synthesis of vasodilatory prostaglandins—for example, prostacyclin or prostaglandin $E_2$ or a prostaglandin-like substance. There are data suggestive that preeclampsia may be associated with inappropriately increased production of a prostaglandin with vasoconstrictor properties or either increased inactivation or diminished synthesis or release of another with vasodilator properties or a combination of these events.

## Cardiovascular Changes

Values obtained by invasive cardiovascular monitoring in women with severe preeclampsia and eclampsia have helped to define cardiovascular status. At least five general observations can be made.[31-33]
1) Before treatment, myocardial contractility is rarely impaired. 2) Cardiac afterload is elevated in the absence of therapeutic interventions. 3) Cardiac output varies inversely with vascular resistance.
4) Medications that reduce vascular resistance (for example, hydralazine) result in increased cardiac output. 5) Ventricular preload, measured by central venous and pulmonary capillary wedge pressures, is usually normal or even low in severe preeclampsia and eclampsia, unless substantial volumes of fluids are administered.

Hemoconcentration is common in women with severe preeclampsia or eclampsia, and the intravascular volume expansion that is normal for pregnancy is not present or is reduced significantly.[34] The woman of average size usually has a blood volume of nearly 5,000 mL during the last several weeks of a normal pregnancy, compared with about 3,500 mL when nonpregnant. With preeclampsia or eclampsia, however,

pregnancy-induced hypervolemia either never develops or is reduced significantly after vasospasm ensues. In the absence of hemorrhage, the intravascular compartment in these women usually is not "underfilled," since vasospasm has contracted the space to be filled. Hemoconcentration usually persists a few hours to a few days after delivery when typically the vascular system dilates, the blood volume increases, and the hematocrit falls. *In the woman with severe preeclampsia or eclampsia, therefore, hypertension may be exacerbated and the risk for pulmonary edema increased as the result of vigorous fluid therapy administered in an attempt to expand the contracted blood volume to normal pregnancy levels. Likewise she can become hypovolemic even with normal blood loss at delivery.*

## Hematological Changes

Thrombocytopenia, although infrequently severe, is the most commonly found hematological aberration (by routine clinical testing) associated with hypertension in pregnancy. Fibrin degradation products in serum are elevated only occasionally. Unless there is some degree of placental abruption, plasma fibrinogen does not differ remarkably from levels found late in normal pregnancy.[35]

Antithrombin III levels are lower and fibronectin levels higher in women with preeclampsia compared with normal pregnant women; these levels are consistent with vascular endothelial injury.[36,37] The clinical utility of serial antithrombin III or fibronectin measurements for the diagnosis and management of preeclampsia awaits further evaluation.

The development of overt thrombocytopenia, that is, a platelet count less than 100,000 per μL, is an ominous sign in women with preeclampsia. Without delivery, the platelet count most often continues to decrease and may reach levels that can result in cerebral or subcapsular hepatic bleeding as well as excessive blood loss during and after delivery, especially by cesarean section. *Maternal thrombocytopenia is not an indication for cesarean delivery.*

The cause of the thrombocytopenia is not firmly established. It has been ascribed to platelet deposition at sites of endothelial damage[35] or to an immunological process.[38] There is no firm evidence that the fetuses-infants born to women with severe preeclampsia-eclampsia will develop thrombocytopenia, despite severe maternal thrombocytopenia.[39]

## Renal Changes

The majority of women with preeclampsia experience mild to moderately diminished renal perfusion and glomerular filtration with correspondingly elevated plasma creatinine and uric acid levels. An elevated plasma creatinine is a late development in the evolution of preeclampsia and is often discerned only in the range that would be considered normal for nonpregnant individuals, for example, 0.8 to 1.0 mg/dL. In some cases of severe preeclampsia, renal involvement may be profound, and plasma creatinine may be elevated two- to threefold over normal values in nonpregnant women. This probably is due to intrinsic renal changes.[40] In unusual instances, preeclampsia may lead to acute tubular, and even cortical, necrosis.

Although some degree of proteinuria should be found for the diagnosis of preeclampsia-eclampsia to be reliable,[41] proteinuria usually develops late in the course of the disease, so some women may be delivered before it appears. Thus, they may have "true preeclampsia" without proteinuria. This type of proteinuria is nonselective; the increased permeability includes proportionally more of larger molecular weight proteins such as transferrin and several globulins than in renal diseases with selective proteinuria. Thus, abnormal albumin excretion is accompanied by increased

quantities of many other proteins. Proteinuria usually recedes within a week following delivery and resolution of hypertension, but in exceptional cases the protein leak may take over a month to heal.

Renal changes identifiable by light and electron microscopy include those in the capillary loops, which are variably dilated and contracted. The endothelial cells are swollen; deposited within and beneath these cells are fibrils, which have been mistaken for thickening and reduplication of the basement membrane. Electron-microscopic studies are consistent with the view that the characteristic changes are caused by swelling of *intraglomerular* cells, primarily of endothelial cells but on occasion mesangial cells. These changes, which may be accompanied by subendothelial deposits of a fibrin-like protein material, are termed *glomerular capillary endotheliosis*.[40,42]

## Hepatic Changes

Severe preeclampsia may result in alterations in tests of hepatic function and integrity, including elevation of serum aspartate aminotransferase levels. The lesion most likely to account for hepatic impairment is *periportal hemorrhagic necrosis*. Bleeding from these lesions may extend beneath the hepatic capsule to form a *subcapsular hematoma*. Hepatic involvement in preeclampsia-eclampsia is serious, and it frequently is accompanied by evidence of involvement of other organs, especially the kidney and brain, along with hemolysis and thrombocytopenia.[43]

## Changes in the Brain

The principal postmortem lesions described in the brains of women who died with eclampsia are hyperemia, focal anemia, thrombosis, and hemorrhage.[44] Cerebral blood flow, oxygen consumption, and vascular resistance were reported as not altered in women with preeclampsia,[45] but the possibility of focal blood flow changes could not be excluded. However, cerebral oxygen consumption is reported to be decreased by 20 percent in eclampsia with normal blood flow, such that McCall[45] alluded to it as "histotoxic hypoxia." Nonspecific abnormalities in the electroencephalogram are common in eclamptic women within 48 hours of seizures, but the tracings are usually normal by 3 months.[46]

Until recently, cranial computed tomographic scans usually were reported to be normal in women with otherwise uncomplicated eclampsia. However, with more advanced equipment, nearly half of eclamptic women have abnormal radiographic findings.[47] The most common of these findings are hypodense areas, frequently seen in the cortical areas, that correspond to areas of petechial hemorrhage and infarction.[48]

While visual disturbances are common with severe preeclampsia, blindness—either alone or accompanying convulsions—is uncommon. Women with *amaurosis* of varying degrees usually have computerized tomographic evidence of extensive occipital lobe hypodensities. These women completely recover within a week. *Retinal detachment* also may cause altered vision, although it is usually one-sided and seldom causes total vision loss. Even without surgical treatment, vision usually returns to normal within approximately a week.

## Uteroplacental Perfusion

Compromised placental perfusion due to placental pathology (failure of trophoblastic invasion of spiral arteries) and vasospasm is almost certainly a major culprit in the genesis of increased perinatal morbidity and mortality associated with preeclampsia. However, there are formidable problems to measuring uteroplacental blood flow in humans with preeclampsia. In an earlier study,[49] it was observed that $^{24}Na$ injected into the intervillous space was cleared two to three times more rapidly in normotensive

pregnant women than in preeclamptic women, implying decreased uteroplacental perfusion.

These findings are supported indirectly by studies of the clearance rate of dehydroisoandrosterone sulfate through placental conversion to estradiol-17ß. More recently, measurement of the velocity of blood flowing through the uterine arteries has been used to estimate uteroplacental blood flow. Using arterial velocity waveforms obtained by Doppler ultrasound, vascular resistance is estimated by comparing systolic and diastolic waveforms. Normally, the uterine vascular bed is a low-resistance circuit and flow continues throughout diastole. As resistance increases, diastolic velocity diminishes in relation to systolic velocity, and this relationship is used to estimate decreased flow. Some investigators report an increased systolic-diastolic ratio in uterine arteries of women with preeclampsia.[50,51] It should be emphasized that the aforementioned methods do not measure perfusion.

# Differential Diagnosis of Hypertension in Pregnancy

Discussions concerning the clinical spectrum of the hypertensive disorders in pregnancy relate to those symptoms, signs, and laboratory aberrations that permit differentiation of preeclampsia (pure or superimposed) from the more benign forms of high blood pressure, mainly essential and gestational (or transient) hypertension.

The need to distinguish preeclampsia from other disorders is particularly important in the management of women presenting in midpregnancy (prior to gestational week 28) and in counseling about future pregnancies. With respect to the former, patients with midterm elevations in blood pressure secondary to essential hypertension may be managed conservatively even when they present with moderate to severe degrees of hypertension. However, attempts to temporize in the presence of severe preeclampsia can be disastrous, as shown by Sibai et al.[52] These authors attempted conservative therapy in 60 consecutive gravidas presenting with severe preeclampsia between the 18th and 27th gestational weeks. Perinatal mortality was 87 percent. Ten mothers convulsed, two developed hypertensive encephalopathy, and one had an intracerebral hemorrhage. In addition, there were five instances of severe coagulopathy, one resulting in a ruptured capsular hematoma of the liver, and three women developed acute renal failure. While there are still dissenting opinions, most authorities consider temporization of *severe* midterm preeclampsia too risky, and interruption of gestation is usually in the mother's best interest.

The second reason for establishing a correct diagnosis relates to counseling. Subsequent pregnancies are often apt to be normotensive when preeclampsia-eclampsia develops in nulliparous women, whereas preeclampsia (or high blood pressure due to other causes) in a multipara is associated with a greater likelihood of hypertension in subsequent gestations. In summary, when hypertension complicates pregnancy, establishing an accurate diagnosis may be useful both to help clinicians assess the immediate well-being of mother and fetus and to counsel her when she seeks advice on future pregnancies.

Results from renal biopsy studies underscore the difficulty in distinguishing clinically between preeclampsia (pure or superimposed) and other causes of high blood pressure in pregnancy. Investigators continue to seek sensitive and specific tests with which to make this differentiation.[1,19] Some tests now of historical interest only include demonstration of decreased fractional urate clearance; reduced sodium excretory capacity after infusions of hypertonic saline; and exaggerated pressor responses to vasopressin or after changing from lateral recumbency to a supine posture (the "rollover" maneuver). These tests have proved unreliable or have insufficient specificity to make them clinically useful.[1]

Several additional approaches that might help in the correct diagnosis of pure or superimposed preeclampsia have been proposed recently. These include measurements of plasma antithrombin III,[53] serum iron and carboxyhemoglobin,[54] and urinary excretion of calcium.[55] Currently, however, the validity of these approaches has not been

proven* and some have been challenged.[56] Other tests under study are detection of antibodies to laminin[57] and identification of serum factors that increase mitogenic activity in fibroblasts or are toxic to endothelial cells in culture.[58,59]

## Recommended Laboratory Tests

Laboratory tests may aid in the diagnosis and management of hypertension during pregnancy. They also provide reference data when high-risk patients first present for prenatal care.

### High-Risk Patients Presenting With Normal Blood Pressure

Gestations in women presenting with normal blood pressure but at high risk include women with a history of increased blood pressure when not pregnant, those who have had hypertension in a previous pregnancy other than the first, and those with diabetes, collagen vascular disease, or underlying renal vascular or renal parenchymal disease (see section on Blood Pressure in Normal Pregnancy and the Epidemiology of Hypertensive Disorders). Certain baseline data, when compared with results obtained in later gestation, will assist in the early diagnosis of preeclampsia. Baseline data in such women should include hematocrit, hemoglobin, and platelet count as well as serum creatinine and uric acid levels. If routine urine analysis demonstrates qualitative proteinuria of 1+ or greater, a 24-hour collection should be obtained, including determination of creatinine content to check for accuracy of measurement and to permit calculation of the creatinine clearance. Some might include serum albumin and serum oxaloacetic transaminase determinations in the baseline assessment, while others would seek these tests only in the presence of frank hypertension. These patients should also undergo ultrasonography at their initial visit for accurate dating and as a baseline for evaluating subsequent fetal growth.

### Patients Presenting With Hypertension Prior to Gestation Week 20

Most women presenting with hypertension prior to gestation week 20 have (or will develop) essential hypertension, and their management is discussed in the next section. Some of these patients will be under the care of primary physicians and will have been screened for signs of secondary hypertension. If not, we recommend the approach to hypertension evaluation and diagnosis suggested in the JNC IV.[7] Finally, gravid women with preexisting or early gestational hypertension are among the population where secondary hypertension is more apt to be found, e.g., renal disease, renovascular hypertension, primary aldosteronism, Cushing's syndrome, and pheochromocytoma. Thus, further evaluation is warranted even for minimal suspicion. For example, pheochromocytoma, although rare, has a propensity to manifest or be activated by pregnancy, and it is associated with high maternal mortality when undiagnosed.[60,61] Thus, suspicion warrants performance of a screening test to detect pheochromocytoma—for example, 24-hour excretion rate of vanillylmandelic acid (VMA) or metanephrines, or plasma norepinephrine and epinephrine levels.

Baseline determinations of renal function (serum creatinine, uric acid) and platelet count can be compared with values in later pregnancy to help determine if blood pressure increases at this time are the usual physiological increase in blood pressure or the onset of preeclampsia. Since these fetuses are at high risk for the development of intrauterine growth retardation, baseline

* Studies designed to detect preeclampsia are currently hampered by the fact that renal biopsies are rarely indicated today, and absence of morphologic correlations makes it difficult to assess the true sensitivity and specificity of test results.

sonography for dating and fetal size are indicated prior to 20 weeks gestation.

## Patients Presenting With Hypertension After Midpregnancy

Table 1 summarizes the laboratory evaluation of women with hypertension after midpregnancy and the rationale for testing them biweekly or more often if clinical circumstances lead to hospitalization of the patient. It is important to recognize that one or more of these abnormalities may be present even when blood pressure elevation is minimal. If there is a life-threatening abnormality such as coagulopathy or abnormal hepatic or renal function, it may be necessary to terminate the pregnancy despite only mild hypertension (see section on Management of Preeclampsia).

**Table 1**

**Laboratory Evaluation of Women Who Develop Hypertension After Midpregnancy**

| Test | Rationale |
|---|---|
| Hemoglobin and Hematocrit | Hemoconcentration supports diagnosis of preeclampsia and is an indicator of severity. Values may be decreased, however, if hemolysis accompanies the disease. |
| Blood Smear | Signs of microangiopathic hemolytic anemia (e.g., schistocytes) favor diagnosis of preeclampsia, and may be present when blood pressure is only mildly elevated. |
| Platelet Count | Decreased levels suggest severe preeclampsia. |
| Urinalysis | If qualitative dipstick is 1+ or greater, a quantitative measurement of protein excretion should be done. Hypertensive gravidas with proteinuria should be considered preeclamptic (pure or superimposed) until proven otherwise. |
| Serum Creatinine Level | Abnormal or rising levels, especially when associated with oliguria, suggest severe preeclampsia. |
| Serum Uric Acid Level | Increased levels aid in the differential diagnosis of preeclampsia and are an indicator of disease severity. |
| Serum Oxaloacetic Transaminase | Abnormal values suggest severe preeclampsia with hepatic involvement. |
| Lactic Acid Dehydrogenase | Elevated levels are associated with both hemolysis and hepatic involvement and suggest severe preeclampsia. |
| Serum Albumin | Values may be decreased even in the absence of heavy proteinuria and may relate to "capillary leak" or hepatic involvement in preeclampsia. |

# Management of Hypertension in Pregnancy

## Management of Preexisting Chronic Hypertension in Pregnancy

### Counseling

Hypertensive women considering pregnancy should be counseled prior to conception. They should be informed of the high likelihood of a favorable outcome in most cases of mild to moderate essential hypertension. They should be aware of the increased risk of superimposed preeclampsia and of the possible complications if preexisting renal disease or systemic illness is present.

It is helpful to inform women prior to pregnancy of possible adjustments in lifestyle that may be necessary during pregnancy if the blood pressure is elevated—specifically, the possibility that restricted activity, bed rest, or even hospitalization may be advisable.

Patients with intrinsic renal disease who are normotensive and have minimal renal dysfunction usually do well in pregnancy. However, those with azotemia (creatinine >2 mg/dL or some say 1.5 mg/dL) and hypertension should be advised of a number of risks.[62,63] These include a high incidence of superimposed preeclampsia, increased perinatal morbidity and mortality, and the possibility that maternal renal function may deteriorate further as a result of the pregnancy.[63,64] These concerns are especially applicable to women with renal transplants, in whom pregnancy should be undertaken only after consultation with a nephrologist with expertise in this area.

## Nonpharmacologic Treatment of Chronic Hypertension

Close medical supervision is the mainstay of management of pregnant women with chronic hypertension. It is preferable to control the blood pressure without medication when possible. In patients with diastolic blood pressure from 90 to 99 mm Hg, this goal is not difficult to attain, since blood pressure falls in most pregnant women during the first and second trimesters.

The strategies for nonpharmacologic therapy of hypertension during pregnancy differ from those in nonpregnant individuals. Whereas weight reduction and exercise might benefit a nonpregnant individual, these measures are not encouraged during pregnancy. Although there are no studies that address the issue of exercise in hypertensive pregnancy, given the theoretical concerns regarding the role of the uteroplacental blood flow in the pathogenesis of preeclampsia, women with chronic hypertension should not be encouraged to participate in vigorous exercise.

#### *Restriction of Activity*

Bed rest is a good means of maximizing uteroplacental blood flow during pregnancy and is considered established therapy in preeclampsia. In chronic hypertension, its effectiveness has not been well studied, but it is an integral feature of management. Rest has been shown to reduce premature labor, lower blood pressure, and promote diuresis.[65] Strict bed rest is rarely necessary. However, all pregnant women with elevated blood pressure, whatever the cause, should be advised to limit their activities when possible and set aside time during the day

when they can be "off their feet." Although many women may find it difficult to restrict their activity, it is helpful to explain the benefits to the patient prior to pregnancy so she can make adjustments in child care, her job, and other responsibilities. In patients with mild to moderate hypertension, restriction of activity may be effective in lowering blood pressure, and antihypertensive medications may be avoided. In patients with severe hypertension, it is usually advisable to hospitalize them for bed rest and medication when necessary.

### *Diet*

Weight reduction may be helpful in reducing blood pressure in nonpregnant individuals, but it cannot be recommended during pregnancy. If a hypertensive woman is overweight and planning a pregnancy, then weight reduction prior to pregnancy is advisable.

Hypertensive pregnant women have lower plasma volume than normotensives, and some studies suggest that the severity of hypertension correlates with the degree of plasma volume contraction.[66] For this reason, sodium restriction is generally not recommended during pregnancy.[67] If, however, a pregnant women with chronic hypertension is known to have salt-sensitive hypertension and she has been successfully treated with a low-salt diet prior to pregnancy, then it is reasonable to continue some sodium restriction during pregnancy. Patients with renal disease and reduced creatinine clearances are more likely to require sodium restriction for blood pressure control, and this should be continued during pregnancy. The amounts of weight gained during the pregnancy may be an indication of whether salt intake is appropriate.

Preliminary studies have shown that dietary calcium supplementation lowers blood pressure in pregnant and nonpregnant individuals.[68,69] However, there are insufficient data to recommend its use for hypertension treatment.

### *Home Blood Pressure Monitoring*

The rationale for close observation of the pregnant hypertensive woman is that changes in clinical status (such as development of superimposed preeclampsia) can be recognized before they become severe. This is easier to accomplish if patients are instructed to take their blood pressures at home and keep a record of the readings. They can then contact medical personnel if the blood pressure rises significantly before a scheduled visit. Home monitoring of blood pressure is often helpful since it will enable the patient to determine how much limitation of activity is necessary to keep her blood pressure controlled. This technique also helps discriminate truly elevated blood pressure from labile blood pressure increases common in young patients. Patients who are candidates for home blood pressure monitoring should have formal instruction on the correct technique for blood pressure determination. In addition, their equipment should be periodically checked for accuracy. Preliminary data on home blood pressure monitoring during pregnancy suggest that it is a useful adjunct to the care of the pregnant woman.[70]

### *Alcohol and Tobacco*

The use of alcohol and tobacco during pregnancy should be discouraged strongly. Both have a deleterious effect on the fetus and mother. Excessive consumption of alcohol can aggravate hypertension or raise blood pressure in the mother de novo.

## Rationale for Pharmacologic Treatment

The majority of women with chronic hypertension in pregnancy have mild to moderate elevations in blood pressure, and therefore the risk of acute cardiovascular complications is extremely low. In the small percentage of women who have severe hypertension, the increased risk of cerebral hemorrhage, cardiac failure, and myocardial

infarction necessitates close monitoring and aggressive treatment during pregnancy.

Although there is increased perinatal morbidity and mortality when the mother has chronic hypertension,[1,71,72] most pregnancies in these women result in healthy, full-term infants. Women with chronic hypertension are at increased risk of developing superimposed preeclampsia, and there is evidence that most, if not all, of the increased perinatal morbidity and mortality associated with chronic hypertension is attributable to this complication.[73] The literature is conflicting, however. Some studies have shown that babies born to women with chronic hypertension in pregnancy who do *not* develop superimposed preeclampsia do as well as those born to normotensive women.[73] Other studies report a higher perinatal loss in uncomplicated hypertensive pregnancy (compared with normotensive), especially with higher levels of blood pressure.[1]

The objective in treating a pregnant woman with chronic hypertension is to minimize the short-term risks to the mother of elevated blood pressure while avoiding therapeutic maneuvers that compromise fetal well-being. The specific goals for the mother are to prevent cardiovascular complications of severe hypertension and, if possible, to prevent preeclampsia. When maternal blood pressure reaches diastolic levels of ≥100 mm Hg, treatment should be instituted to avoid hypertensive vascular damage. Some experts feel at least nonpharmacologic treatment is warranted at diastolic blood pressures of ≥90 mm Hg.

The indications for treatment of hypertension (at diastolic blood pressures of 90-99 mm Hg) during pregnancy are less clear. In the nonpregnant individual, treatment of mild to moderate hypertension is recommended for prevention of long-term cardiovascular consequences of elevated blood pressure.[7]

To date, clinical trials and clinical experience have not given us a conclusive answer to the question, "Does treatment of chronic hypertension prevent preeclampsia?" Many of the clinical trials of antihypertensive therapy in chronic hypertension have evaluated treatment begun in the third trimester.[74-76] This is largely a consequence of the fact that blood pressure falls in most women during the first trimester, reaching its nadir by midpregnancy. This phenomenon occurs in chronic hypertensives as well, and since most patients have only mild hypertension to begin with, by midpregnancy the majority will be normotensive. Therefore, it is frequently not until the third trimester, when the blood pressure rises, that treatment is begun. If superimposed preeclampsia in the chronic hypertensive is associated with the same placental pathology as in pure preeclampsia, then the definitive morphological changes are already present by 20 weeks. Thus one would not expect antihypertensives begun in the third trimester to alter these changes. To complicate matters, patients enrolled in clinical trials that have started treatment in the third trimester are frequently a heterogeneous population—and include patients with transient hypertension, preeclampsia, and chronic hypertension.

There are almost no data available that would either support or dispute the notion that early treatment of chronic hypertension (in the first half of pregnancy) prevents superimposed preeclampsia. Carefully conducted clinical trials are needed to resolve this issue.

It is not uncommon for a pregnant woman with chronic hypertension to be hospitalized because of elevated blood pressure. Early treatment of hypertension in pregnancy may reduce the need for such hospitalization, but it may obscure the diagnosis of superimposed preeclampsia, since a rise in blood pressure may be the first sign of this condition.[77] It is particularly important to monitor women being treated for hypertension

during pregnancy for signs of preeclampsia since this condition is associated with adverse fetal outcome.

With regard to fetal well-being, several studies suggest, but do not conclusively demonstrate, benefits of treating mild to moderate hypertension during pregnancy.[78] In the largest published clinical trial demonstrating a reduction in perinatal mortality in mothers treated with methyldopa, the major intake of patients was during the second trimester, with a significant proportion entering earlier in the first half of pregnancy.[79] Since the beneficial outcome was due to a decrease in midtrimester pregnancy losses, it is not clear whether lowering blood pressure was responsible for the improved outcome. Given the potential hazards of antihypertensive treatment during pregnancy (the possibility that medication may reduce placental blood flow, or adversely affect the fetus) treatment of hypertension (at diastolic levels of 90-99 mm Hg) must be undertaken cautiously, weighing the risks and benefits of treatment for both mother and child at all times. Excessive blood pressure reduction is to be avoided, and a conservative approach is recommended.

## Drug Treatment of Chronic Preexisting Hypertension

The goal of treating chronic hypertension during pregnancy is the reduction of maternal risk and perhaps that of the fetus (see section on Management of Preexisting Chronic Hypertension in Pregnancy). With this goal in mind it is mandatory to establish not only the efficacy of drugs to reduce blood pressure but also the acute and long-range effects of these drugs on fetal well-being, especially (based on the mechanism of action of many antihypertensive drugs) long-range neurological effects. So far only one drug—methyldopa—meets these criteria. Thus, if feasible, methyldopa therapy should be chosen in pregnancy. If this drug is ineffective or cannot be tolerated (which happens not infrequently), alternative therapy is determined by guidelines based on limited clinical experience and rational choices based on the mechanisms by which the drugs act. It is important to point out that, in spite of theoretical concerns, none of the drugs currently used to treat hypertension other than the angiotensin converting enzyme (ACE) inhibitors have been demonstrated to increase perinatal morbidity or mortality within the limits of acute followup. The following categories of antihypertensive agents are addressed alphabetically.

### *Angiotensin Converting Enzyme Inhibitors*

This new class of antihypertensive agents, which act in part by inhibiting conversion of angiotensin I to angiotensin II, has become popular in the treatment of essential hypertension and hypertension associated with renal disease in nonpregnant patients because of its minimal side effects. Although no teratogenic effects have been observed in animals using these drugs, they do lower uterine blood flow and reduce fetal survival in pregnant rabbits and sheep, perhaps by decreasing uterine $PGE_2$ and $PGI_2$ synthesis.[80] Acute renal failure with lethal consequences has also been described in the neonates of women treated with ACE inhibitors in the last trimester.[81-84] Because other antihypertensive agents are available, it is recommended that ACE inhibitors should be avoided during pregnancy.

### *Beta-Adrenergic Blocking Agents*

Evidence is accumulating that beta-adrenergic blocking drugs are useful and sufficiently safe in treating preexisting hypertension during pregnancy.[78,85] There is also evidence that the combined alpha- and beta-blocking agent labetalol (alpha and beta antagonism ratio 1:4) is relatively safe and effective in pregnancy.[85-88] Most studies to date demonstrate equal effectiveness when beta adrenoreceptor antagonists and the combined alpha- and beta-blocker labetalol are compared to methyldopa.[85]

Finally, despite a growing and reassuring literature of controlled trials with beta and combined beta and alpha adrenoreceptor agents, we must interject a note of caution. Most studies were relatively small and gestational age at entry was usually 29 to 33 weeks, leaving unanswered the possibility that treatment of larger numbers of patients and/or a longer duration of drug administration may reveal adverse effects.[87,89] For instance, Butters et al.[89] suggest that the long-term use of beta-blockers predisposes to major growth retardation. Finally, while some prefer beta-adrenergic blockers because they cause less somnolence than methyldopa, others continue to favor the $alpha_2$ agonists because of concern that beta-blocking agents, which cross the placenta, may interfere with interpretation of fetal heart rate as well as because of the theoretical possibility that beta-blockers compromise the ability of the fetus to withstand hypoxic stress.

### *Calcium Channel Blockers*

Calcium channel blockers have been used to treat essential hypertension for many years in Europe and recently have been introduced into the United States. Nifedipine, which has a greater effect on vascular smooth muscle than on the myocardium, has proven promising in treating hypertension. However, it is teratogenic in rats when given in doses 30 times the maximum recommended human dose. There are very few studies of its use throughout human pregnancy, although these drugs are used in later pregnancy as treatment for preterm labor without adverse consequences.[90,91]

### *Centrally Acting Adrenergic Inhibitors*

Methyldopa and clonidine are the two most commonly used central adrenergic antagonists, and both are used during pregnancy.[92-94] Clonidine is a centrally acting adrenergic inhibitor that inhibits sympathetic output from the central nervous system. The effect of methyldopa is more complex, but it also inhibits central sympathetic discharge. Methyldopa was the first antihypertensive agent used in the treatment of hypertension during pregnancy, so the experience with it is the longest. Followup studies of children born to mothers taking methyldopa throughout pregnancy have revealed normal mental and physical development in these children at 10 years of age.[95] Methyldopa given to women with essential hypertension has been demonstrated to reduce the number of midtrimester abortions without affecting neonatal survival or fetal growth.[79]

Methyldopa causes somnolence in many individuals. However, its demonstrated safety for the fetus in long-term followup[95] makes this the initial drug of choice in the management of chronic hypertension in pregnant women and the benchmark against which other antihypertensive agents must be tested.

### *Diuretics*

The use of diuretic agents in pregnancy is controversial. The primary concern is theoretical. It is known that preeclampsia is associated with a reduction of plasma volume[96] and that fetal outcome is worse in chronically hypertensive women who fail to expand plasma volume.[97] Whether this is a cause-and-effect relationship is not clearly established. Nonetheless, women using diuretics from early pregnancy do not increase their blood volume to the degree usually occurring in normal pregnancy.[98] This theoretical concern must be tempered by extensive experience in several well-controlled studies with the prophylactic use of diuretics in normotensive gravidas in which no excess of perinatal mortality or morbidity was evident.[99] A meta-analysis of nine randomized trials comprising over 7,000 subjects revealed a decrease in the tendency of these women to develop edema and/or hypertension[100] and confirmed no increased incidence of adverse fetal effects. Based on the theoretical concerns, diuretics are usually not used as first-line drugs. However, if their use is indicated, they are

safe and efficacious agents, can markedly potentiate the response to other antihypertensive agents, and are not contraindicated in pregnancy except in settings where uteroplacental perfusion is already reduced (preeclampsia and intrauterine growth retardation).

Although data concerning the use of diuretics in pregnant women with essential hypertension are sparse, this committee concluded that gestation does not preclude use of saluretic drugs to reduce or control blood pressure in women whose hypertension predated conception or manifested prior to midpregnancy. (The JNC IV recommended smaller doses of diuretics than used previously, thus minimizing metabolic effects.[7])

*Vasodilators*

Hydralazine is a vasodilator that is relatively ineffective when used alone because of the reflex tachycardia with increased cardiac output that occurs with its use. However, when hydralazine is combined with a beta-adrenergic blocking agent, the reflex tachycardia is prevented, and the combination is quite effective in reducing blood pressure. Hydralazine is used extensively, usually with methyldopa, in treating preexisting hypertension in pregnancy and is considered to be safe for mother and fetus by most obstetricians. Still, one survey in Scandinavia has reported fetal thrombocytopenia.[101] Therefore, its use as a first-line drug in treating pregnant women with chronic preexisting hypertension should be limited.

*Summary*

Although this working group endorses judicious antihypertensive therapy for pregnant women with preexisting essential (chronic) hypertension (diastolic blood pressures of ≥ 90 mm Hg), there is no good existing evidence that the use of antihypertensive therapy improves fetal survival. Methyldopa may prevent midgestational losses.

### Maternal-Fetal Surveillance

Whether the patient has acute or chronic hypertension, fetal surveillance is indicated. The methodology for fetal surveillance is the same in both cases and the interpretation is similar. If the fetus is compromised, then decisionmaking and judgment are necessary. If intrauterine growth retardation is identified by fundal measurements and documented by ultrasound, biophysical testing should be implemented. The amount of amniotic fluid is significant since a decreased amount of fluid may be associated with cord problems during labor.

Nonstress testing, oxytocin challenge testing, ultrasound, and fetal movement counts constitute the most common fetal surveillance techniques. If determination of pulmonary maturity would influence management, amniocentesis should be done to determine this prior to the interruption of pregnancy.

Fetal surveillance involves determining if the fetus is growing appropriately. When fundal height measurements are inappropriate, other investigative avenues such as ultrasound biophysical testing should then be pursued. As long as the fetus continues to grow in an appropriate manner, it can be inferred that the placenta and/or uterine blood flow are appropriate.

## Management of Preeclampsia

### Prevention of Preeclampsia

Our ability to prevent preeclampsia is limited by lack of knowledge regarding its cause. The cornerstone of "prevention" in preeclamptic patients has been identification of the high-risk individual (see section on Blood Pressure in Normal Pregnancy and the Epidemiology of Hypertensive Disorders), followed by close clinical and laboratory monitoring so that the disease process can be recognized in its early stages. Women can

then be hospitalized for more intensive monitoring or delivery. While these measures do not enable us to prevent preeclampsia, they do help to prevent its catastrophic maternal and fetal sequelae.

Although various dietary and pharmacologic strategies (low-salt, high- or low-protein diet; diuretics) have been employed with the hope of preventing preeclampsia or minimizing its severity, none have proved effective so far. Many obstetricians consider daily rest to be effective in preventing preeclampsia or minimizing its severity in high-risk individuals, although this has not been proven.

One preventive strategy that is currently receiving a great deal of attention is the use of low-dose aspirin. At the present time many centers around the world are investigating the ability of low-dose aspirin to prevent preeclampsia. These clinical trials have been prompted by two initial encouraging reports.[102,103] In both trials, low-dose aspirin[103] or low-dose aspirin plus dipyridamole[102] was successful in reducing the incidence of preeclampsia in the groups studied. There were no fetal or maternal complications attributable to aspirin in either study; however, the total number of women who received aspirin was fewer than 100. Two recently published trials of low-dose aspirin in moderate- and high-risk pregnant women support these earlier encouraging reports and provide evidence that the beneficial effects of aspirin are associated with selective inhibition of platelet thromboxane $A_2$ generation, with preservation of vascular prostacyclin generation.[104,105] However, since aspirin in large doses is associated with hemorrhagic complications in the newborn,[106] and since prostaglandins play a major role in maternal-fetal physiology, we do not recommend treatment of women at risk for preeclampsia with low-dose aspirin until large clinical trials have conclusively documented the safety and efficacy of this therapy.

## Rationale for Treatment

The objectives of therapy for preeclampsia are based on a philosophy of management arising from the knowledge of the pathology and pathophysiology and the prognosis of the disorder for mother and baby.

- **Delivery is always appropriate therapy for the mother but may not be so for the fetus.** For maternal health, the goal of therapy is to prevent eclampsia *as well as other severe complications of preeclampsia.* Preeclampsia is the precursor of eclampsia, and careful antepartum observation can identify the woman at risk. Preeclampsia is completely reversible and begins to abate with delivery. Thus, if only maternal well-being were considered, the delivery of all preeclamptic women, regardless of severity of the process or stage of gestation, would be appropriate. Considering the fetus, however, one ought not induce delivery in mildly preeclamptic women whose fetuses are immature but have no signs of fetal compromise. There are two important corollaries of this statement. First, any therapy for preeclampsia other than delivery must have as its successful endpoint the reduction of perinatal mortality and morbidity. Second, the cornerstone of obstetric management of preeclampsia is based on a decision as to whether the infant is more likely to survive in utero or in the nursery.
- **The signs and symptoms of preeclampsia are not of pathogenetic importance.** The pathologic and pathophysiologic changes of preeclampsia indicate that poor perfusion is the major factor leading to the derangement of maternal physiologic function and to increased perinatal mortality and morbidity rates.

  Attempts to treat preeclampsia by natriuresis or by the lowering of blood pressure do not alleviate the important pathophysiologic changes. In fact, natriuresis may be counterproductive and may adversely affect fetal outcome because

plasma volume is already reduced in preeclamptic women.

- **The pathogenetic changes of preeclampsia are present long before clinical criteria leading to the diagnosis are manifest.** Several studies indicate that changes in vascular reactivity, plasma volume, and renal function antedate, in some cases by months, the increases in blood pressure, protein excretion, and sodium retention. These findings suggest that irreversible changes affecting fetal well-being may be present prior to the clinical diagnosis. This possibility probably explains why dietary, pharmacologic, and postural therapy are not successful when avoidance of perinatal morbidity and mortality is taken as the endpoint. If a rationale for modes of therapy other than delivery of the fetus exists, it would be to palliate the maternal condition in order to allow fetal maturation. However, even this rationale is controversial.

Accelerated and severe hypertension can complicate any phase of gestation. Fortunately, most of these crises occur late in pregnancy and are associated with preeclampsia; the challenge to the physician is to maintain maternal blood pressure at safe levels while effecting a delivery.

## Nonpharmacological Management

### *Maternal Evaluation*

Antepartum monitoring of the mother has two goals. The first is the early recognition of the condition because infants of mothers with even mild preeclampsia are at increased risk, and the second is to gauge the rate of progression of the condition, both to prevent eclampsia by delivery and to determine whether fetal well-being can be safely monitored by the usual intermittent observations. Ideally, identification of early changes would allow intervention prior to the advent of clinical symptoms. At present, other than the early increased sensitivity to angiotensin II, which is not practical for application to widespread screening, no test has a predictive value sufficient to use clinically. Notably unsuccessful are the "rollover test" and elevated second trimester blood pressures.

At present, clinical management is dictated by the overt clinical signs of preeclampsia. Unfortunately, proteinuria—the most valid clinical indicator of preeclampsia—is often a late change, sometimes even preceded by seizures, and so is not a useful sign for early recognition. Although rapid weight increase and facial and digital edema indicate the fluid and sodium retention characteristic of preeclampsia, they are neither universally present nor uniquely characteristic of preeclampsia. These signs are, at most, a reason for closer observation of blood pressure and monitoring of urinary protein. Early recognition of preeclampsia is based primarily on diagnostic blood pressure increases in the late second and early third trimesters relative to early pregnancy. Using blood pressure changes without evidence of proteinuria as an indicator does, undoubtedly, result in the diagnosis of preeclampsia in some normal women as well as in some with underlying renal or vascular disease. Because the goal of early diagnosis is to identify patients requiring more careful observation, however, overdiagnosis is preferable to underdiagnosis.

Once the blood pressure changes suggestive of preeclampsia appear, an office examination within 24 to 48 hours is strongly recommended, or with selected patients, blood pressure and urinary protein must be checked at home. These measures are directed at determining how fast the condition is progressing in order to ensure that it is not following a fulminant course. Frequency of subsequent observations is determined by these initial observations and the ensuing clinical progression. If the condition appears stable, weekly observations may be appropriate. If it appears to be accelerating, more frequent observations, usually in-hospital, are required. The initial appearance of proteinuria is an especially

important sign of progression and dictates frequent observation, which is best accomplished in-hospital.

If an increasing rate of deterioration is noted, as determined by laboratory findings, symptoms, and clinical signs, the decision to continue the pregnancy is determined day by day. Important clinical signs are blood pressure, urinary output, and fluid retention as evidenced by daily weight increase. Laboratory studies are performed at intervals of no more than 48 hours. These include examination for possible activation of the coagulation system as determined by platelet count, and evaluation of renal function as measured by urinary protein excretion and serum creatinine and urate levels. In addition, subjective evidence of central nervous system involvement—such as headache, disorientation, and visual symptoms—and the presence of hepatic distention, as indicated by abdominal pain and hepatic tenderness, are equally important indicators of worsening preeclampsia.

### *Antepartum Management of Preeclampsia*

There is little to suggest that therapeutic efforts alter the underlying pathophysiology of preeclampsia. Therapeutic intervention is palliative. At best, it may slow the progression of the condition, but more likely, it merely allows continuation of the pregnancy. Bed rest is a usual and reasonable recommendation for the woman with mild preeclampsia, although its efficacy is not clearly established. Strict sodium restriction or diuretic therapy has no role in the prevention or therapy of preeclampsia. In women with marked sodium retention as manifested by significant edema, modest sodium restriction may not alter the course of the disease but may reduce discomfort.

### *Indications for Delivery*

Prolonged antepartum management of women with severe preeclampsia is not practiced in most centers. With improvements in neonatal care, many investigators regard delivery of women with rapidly progressing preeclampsia beyond 30 weeks gestation to be in the best interest of not only the mother but also the fetus. When gestational age is critical (between 25 and 30 weeks), one might consider controlling maternal blood pressure along with meticulous observation of the maternal and fetal condition. Delivery is then indicated by worsening maternal symptoms, laboratory evidence of end-organ dysfunction, or deterioration of fetal condition. Whether this plan of action can effect a decrease in perinatal morbidity and mortality rates is not clear. The use of this approach with even very immature fetuses may only replace a nonviable neonate with an extremely premature one, with the attendant risk of long-range neurologic disability. Such an approach should therefore be attempted only in centers equipped to provide meticulous maternal observation and daily assessment of fetal and maternal condition.

**Fetal Indications.** The major consideration in decisions for delivery should usually be fetal well-being, for the reasons cited. Thus, if the maternal condition is stable, delivery is indicated by signs of abnormal fetal function. If fetal growth and well-being remain normal, pregnancy should proceed to spontaneous labor. If the maternal condition is rapidly deteriorating, however, delivery is indicated for fetal well-being. With maternal deterioration, a reflection of increasingly poor perfusion of brain, kidney, and liver, uteroplacental blood flow is also likely to be compromised. In addition, the predictive value of all tests of fetal well-being is invalidated by rapid changes in the maternal and, hence, fetal condition.

**Maternal Indications.** Although fetal considerations usually dictate the timing of delivery, there are important exceptions. In the rare case in which a choice is made to palliate maternal signs and symptoms in order to allow fetal growth or maturation, such efforts must be abandoned if the maternal condition worsens. Also, a potentially lethal complication of preeclampsia, hepatic rupture, cannot be prevented by any

mode of therapy other than delivery. It has a mortality rate of 65 percent. Thus, the woman with hepatic capsular distention manifested by hepatomegaly, tenderness of the liver, and abnormal hepatic function values should be delivered regardless of fetal well-being or maturity.

### *Route of Delivery*

Vaginal delivery is preferable to cesarean delivery for preeclamptic women. It is desirable, if possible, to avoid the added stress of surgery because of multiple physiologic abnormalities. Palliation for several hours should not increase maternal risk if performed appropriately. Induction should be carried out aggressively and expeditiously once the decision for delivery is made. In gestation remote from term in which delivery is indicated but fetal and maternal condition are stable enough to permit pregnancy to be prolonged 36 hours, glucocorticoids can be safely administered to accelerate fetal pulmonary maturity.

The aggressive approach to induction indicates that amniotomy be performed as soon as possible and a clear endpoint be formulated at the initiation of therapy, usually within 8 to 12 hours of the decision to induce delivery. A trial of induction is warranted regardless of cervical condition. Obviously, if vaginal delivery cannot be effected within the predetermined time frame, cesarean delivery should be considered. Likewise, cesarean delivery is performed for other usual obstetrical indications.

Regional anesthesia such as epidural analgesia offers its usual advantages for vaginal and cesarean delivery *but does carry the possibility of extensive sympatholysis with consequent decreased cardiac output, hypotension, and impairment of already compromised uteroplacental perfusion. This is a common problem with spinal anesthesia, which is felt by most experts to be contraindicated in the preeclamptic woman.* This problem can be avoided by meticulous attention to anesthetic technique and volume expansion. Regional anesthesia is not a rational means to lower blood pressure because it does so at the expense of cardiac output. Likewise, although analgesia with narcotics is not contraindicated and should be used when necessary, there is abundant evidence that attempting to manage or prevent eclampsia with profound maternal sedation is dangerous and ineffective.

## Drug Treatment of Hypertension Related to Preeclampsia

Disagreement exists on whether, and how efficiently, the uteroplacental blood flow is autoregulated. Those who liken the uterine circulation to a rigid conduit incapable of autoregulation caution against precipitous decrements in mean arterial pressure because placental perfusion is already compromised in preeclampsia.[1,2,107] Others[108] prefer a more aggressive approach when treating hypertension. Resolution of this problem awaits perfection of reliable and safe methodology to measure placental perfusion, followed by appropriately designed therapeutic trials. In the interim the following guidelines are recommended.

### *Treatment of Hypertension Remote From Delivery*

As cited in several sections of this report, the palliative management of preeclampsia remote from delivery is controversial. The sole rationale is to allow maturation of the fetus, and if attempted, it must not subject the mother to undue risk. An important part of safe management is control of elevated blood pressure. In the woman with diastolic blood pressure ≥100 mm Hg, risk is sufficient to warrant pharmacological therapy. The therapy is solely for maternal benefit; there is neither theoretical basis nor empiric evidence that such therapy is beneficial to the fetus. If therapy is elected, methyldopa is the drug of choice. If this is not tolerated or is unsuccessful, calcium channel blockers, beta-blockers, or hydralazine are reasonable additions or alternatives. Successful control of blood pressure should not be interpreted

as eliminating risk for mother or baby. No evidence indicates therapy improves fetal well-being or reduces the risk of abruption, disseminated intravascular coagulation, seizures, or other maternal risk. Both maternal and fetal assessment must be meticulously carried out regardless of the degree of blood pressure control.

### *Treatment of Acute Hypertension During Delivery*

In the more usual situation, antihypertensive therapy may occasionally be indicated as acute palliative therapy in the woman in whom delivery is indicated. Antihypertensive agents can be withheld as long as maternal pressure is only mildly elevated. However, persistent diastolic levels of 105 mm Hg or higher should be treated.* When treatment is required, the ideal drug that reduces pressures to a safe level should:

- Act quickly
- Reduce pressure in a controlled manner
- Not lower cardiac output
- Reverse uteroplacental vascular constriction
- Result in no adverse maternal or fetal effects.

The medications used to treat hypertensive crises in pregnancy are summarized in table 2. Details of their pharmacology and safety are discussed elsewhere.[85,107,109]

The current drug of first choice is intravenous hydralazine, which if given cautiously is successful in most instances. It has been shown to be effective against preeclamptic hypertension.[34] Although this is sometimes used as an intravenous (I.V.) infusion, the pharmacokinetics (maximal effect at 20 minutes, duration of action 6 to 8 hours) indicate intermittent bolus injections as more sensible. A 5-mg bolus is given intravenously over 1 to 2 minutes. Twenty minutes later, subsequent doses are dictated by the initial response. Once the desired effect is obtained, the drug is repeated as necessary (frequently in several hours). If a total of 20 mg is administered without therapeutic response, other agents should be considered.

Diazoxide is restricted to the occasional resistant case and should be administered in small doses (30-mg boluses). Preliminary successes have been recorded when calcium channel blockers (e.g., nifedipine) have been used, and in 1989 this group of drugs was undergoing testing.[107,110] One concern about calcium channel blockers, however, is that most patients with acute hypertension during delivery will also be receiving magnesium sulfate (vida infra). Magnesium may potentiate the effects of calcium channel blockers and lead to precipitous decreases in blood pressure. Nifedipine acts rapidly, causing significant reduction in arterial blood pressure within 10 to 20 minutes of oral administration. The onset of antihypertensive activity can possibly be shortened by chewing the capsule or puncturing it with several needle holes before it is swallowed. The principal side effects are headache and cutaneous flushing, but minimal reflex tachycardia may occur. Like vasodilators, calcium channel blockers may cause cessation of uterine contractions. They are used to stop premature labor without maternal or fetal side effects.

Limited data are available on the use of parenteral labetalol (which some advocate as a second-line drug), starting with 10 mg and not to exceed 1 mg/kg, or clonidine. Neither labetalol nor clonidine appears to be more effective than hydralazine. Sodium nitroprusside is chosen only after the failure of hydralazine, diazoxide, calcium channel blockers, labetalol, and clonidine because of cyanide poisoning and fetal death reported in laboratory animals.[111]

* It may, however, be prudent to treat lower levels in certain situations: e.g., the young gravida whose recent diastolic levels were below 75 mm Hg, or the woman with chronic hypertension for many years and in whom hypertensive heart disease may be present.

**Table 2**

**Guidelines for Drug Treatment of Severe Hypertension Near Term or During Labor**

The degree to which blood pressure should be decreased is disputed. Levels from 90 to 104 mm Hg diastolic are recommended (see text).

- Hydralazine administered intravenously is the drug of choice. Use low doses (start with a 5-mg I.V. bolus, then give 5 to 10 mg every 20 to 30 minutes) in order to avoid precipitous decreases. Side effects include tachycardia and headache. Neonatal thrombocytopenia has been reported.
- Diazoxide is recommended for the occasional patient whose hypertension is refractory to hydralazine. Use 30-mg miniboluses since maternal vascular collapse and death have been associated with the customary 300-mg dose. Side effects include arrest of labor and neonatal hyperglycemia.
- Experience with parenteral labetalol is growing, and this drug may replace diazoxide as the second-line drug.
- Favorable results have been reported with calcium channel blockers. However, if magnesium sulfate is being infused, the magnesium ion may potentiate the effect of calcium channel blockers, resulting in precipitous and severe hypotension.
- Do not use sodium nitroprusside (fetal cyanide poisoning has been reported in animal models) or diuretics (e.g., furosemide; see text). However, in the final analysis, maternal well-being will dictate the choice of therapy.

Finally, the use of potent saluretic agents such as furosemide in treating hypertensive crises at term, as adjunct therapy to the vasodilators just discussed, is condemned by most authorities but still has its advocates.[108] Given the hemoconcentration and cardiovascular hemodynamics of preeclampsia and the susceptibility of some women with this disease to either intrapartal hypotension or puerperal vascular collapse, many counsel against the use of potent diuretics, and care must be taken with all antihypertensive agents. In the last analysis, however, the mother's well-being should take precedence, even if the therapy necessary to control pressure may potentially harm the fetus.

### *Antieclamptic Therapy*

The pathophysiology of eclampsia is discussed (see section on pathology and pathophysiology of hypertension in pregnancy). It is a mistake to equate the eclamptic convulsion with hypertensive encephalopathy since the convulsion can arise in a seemingly stable patient manifesting only minimal blood pressure elevation. For this reason, many clinicians initiate prophylactic therapy when women with suspected preeclampsia are in labor, even if premonitory signs are absent.

Since the pathogenesis of the eclamptic convulsion is still poorly understood,[107] it is not surprising to find disagreements on how to treat women with impending convulsions or frank eclampsia.[2,107,112-114] Most authorities, especially in North America, use parenterally administered magnesium sulfate; [34] others prefer conventional anticonvulsant drugs such as diazepam and phenytoin. Critics of the use of magnesium sulfate stress that it crosses the blood-brain barrier very slowly[115] and has no effect on electroencephalographic abnormalities.[116] Defense of magnesium sulfate therapy has been mainly empiric, but of interest are recent observations of the effect of magnesium ions on prostaglandin metabolism. For example, Watson et al.[117] have demonstrated that magnesium at levels measured in treated preeclamptics increases prostacyclin release by cultured endothelial cells from human umbilical veins, and that plasma from preeclamptic women treated with magnesium sulfate had similar actions. The

preference for magnesium sulfate, especially in the United States, is documented by its successful use in several large series,[1,34,108,117,118] but it has never undergone a definitive controlled trial. Similarly, there is a need for more extensive data regarding the effect of both magnesium and standard anticonvulsant drugs on the neonate. Preliminary data on the effects of magnesium sulfate on fetuses are encouraging.[119]

### *Volume Expansion Therapy*

Just as there are advocates of saluretic agents, there are claims that volume expansion may reduce blood pressure in selected patients with preeclampsia. This approach derives from observations that plasma volume, cardiac output, and pulmonary capillary wedge pressure (PCWP) may be decreased in this condition, as well as from reports that infusion of colloids decreased blood pressure[33,120] and peripheral vascular resistance,[33] despite increments in intravascular volume. However, the effects of colloid infusion are usually transient, probably because the vasculature in preeclampsia is "leaky,"[121] whereas infusion of crystalloids alone decreases oncotic pressure, which is already depressed in preeclampsia.[122] Such decrements can lead to pulmonary or cerebral edema, especially in the immediate puerperium, when oncotic pressure levels decrease further while central volume and PCWP tend to rise.[31,122] Thus, one should be cautious concerning crystalloid infusions into preeclamptic women during labor, and until a postpartum diuresis is established. Signs suggesting poor renal perfusion (i.e., oliguria) resolve quickly after delivery, and acute renal failure is an unusual complication, even in severe preeclampsia.

### *Other Considerations*

Invasive cardiovascular monitoring may be required in severe or complicated cases, especially during operative procedures. Criteria have recently been proposed for pulmonary artery catheterization in the patient with severe preeclampsia.[123] Many experts, however, believe that these criteria are too broad and find the indications for Swan-Ganz catheterization (a procedure associated with a certain morbidity) relatively uncommon.[124]

## Treating Hypertension Persisting Postpartum

The potential problems of serious compromise of placental perfusion and, in turn, fetal well-being that can be induced by antihypertensive agents are obviated by delivery. If there is a problem after delivery controlling persisting severe hypertension, intermittent intravenous hydralazine can be used repeatedly early in the puerperium to control it. Once repeated blood pressure readings remain near normal, the hydralazine is stopped and treatment with standard oral regimens should be started.

Several other regimens are effective for control of severe postpartum hypertension. These have been discussed in the JNC IV[7] and include infusion of nitroprusside (0.5 to 10 mg/kg/min). Labetalol, 20 to 80 mg by intravenous bolus, lowers blood pressure in 5 to 10 minutes and may be repeated at 10-minute intervals.

Acute hypertensive changes induced by pregnancy usually dissipate rapidly after delivery, certainly within the first several days. If severe hypertension persists more than 3 to 5 days, then the likelihood of underlying chronic hypertension is greatly increased. In these cases, oral antihypertensive therapy is begun before discharge and the woman evaluated in 1 week. For women who were hypertensive before pregnancy, chronic treatment is likely to be necessary. If prepregnancy blood pressure was normal or unknown, it is reasonable to stop oral medication after 3 to 4 weeks and observe the blood pressure at weekly intervals for a month, and at monthly intervals for a year. If hypertension recurs, treatment should be resumed.

## Lactation

Many women who have been chronically hypertensive during pregnancy will have the desire to breast-feed their infant for a period of several weeks to 1 year. The concentrations of most of the antihypertensive drugs have been assessed in human breast milk and plasma[125] after single or multiple dosings, and all agents studied have been detectable in the milk. However, only a few reports have evaluated whether the drug is detectable in the plasma of the breast-fed infant[126-128] or if there is any hemodynamic or adverse effect of the agent on the infant. Furthermore, there have been no clinical trials involving several subjects which have studied the cardiovascular effects of any antihypertensive agent on the breast-fed infant.

In mildly hypertensive mothers who wish to breast-feed for a few months, the clinician may consider withholding medication with close observation of the maternal blood pressure. Following discontinuation of the nursing period, the antihypertensive therapy should be reinstituted as appropriate. For those patients with more severe blood pressure elevation on a single antihypertensive agent, the clinician may consider reducing antihypertensive drug dosage with close observation of both the mother and breast-fed infant. If the mother requires multiple agents for controlling her hypertension, breast-feeding is not advisable.

# Remote Prognosis

## Eclampsia

The weighted average prevalence of hypertension following eclampsia is 23.8 percent, as derived from 53 papers reporting followup studies of 2,637 women.[1] There are only two studies of large series with long-term followup, and they agree that the prevalence of remote hypertension is not increased over that in unselected women matched for age and race. Bryans,[129] at the Medical College of Georgia, followed 335 women for 1 to 44 years (average 14). The average age-specific blood pressures of 168 white women at followup fell in the middle of averages for unselected women in three epidemiologic studies of blood pressure, and there was no excess of cases with diastolic pressures of 90 mm Hg or higher. The average age-specific blood pressures of 167 black women were higher than in white women but were within the range of such pressures in unselected black women.

For an average of 33 years, Chesley et al.[130] followed up 99 percent of the 270 women surviving eclampsia between 1931 and 1951 in the Margaret Hague Maternity Hospital in New Jersey, with all but 3 traced to 1974. Remote deaths among the 206 having had eclampsia as primiparas did not exceed the number expected, as derived from age-specific death rates for American women matched for age and race. Only 29 percent of the remote deaths were associated with hypertensive vascular disease. In contrast, three times the expected number of deaths occurred among the 64 women who had had eclampsia as multiparas, and 80 percent of the deaths were caused by cardiovascular-renal complications. Chronic hypertension had been known to have antedated the eclampsia in several of the women. The lowest expected prevalence of hypertension among 11 epidemiologic studies of blood pressure was reported in the study by Hamilton et al.;[131] therefore, their study was used as the most rigid control. The distributions of diastolic and systolic pressures at an average of 33 years after eclampsia in primiparas were virtually identical to those of the controls matched for age, and there was no excess of hypertensives among the posteclamptic women, whatever blood pressure might be taken as the dividing line. There was an excess of hypertensive cases among the multiparous women.

## Preeclampsia

Many of the numerous papers describing followup studies of women thought to have had preeclampsia have found high prevalences of hypertension, and some authors have believed that preeclampsia may cause chronic hypertension in women who otherwise never would have developed it. It is significant that such "residual" hypertension is more common after multiparous than after primiparous pregnancies, more common after mild than severe preeclampsia, and lowest of all after eclampsia. In a word, the more secure the diagnosis, the lower the rate of ultimate hypertension. In the past, and still in most classifications, the diagnosis of mild preeclampsia is made in women with transient hypertension (see the following section). In the unique study by Fisher et al.[19] the diagnosis of preeclampsia was confirmed by renal biopsy. The prevalence of hypertension at followup was about 10 percent, almost identical to the expected rate

as derived from women in the National Health Survey when matched for age and race.

Thus the prevalence of chronic hypertension following eclampsia[129,130] or preeclampsia[19] in primigravidas is the same as in unselected women matched for age and race. Preeclampsia-eclampsia is an intercurrent event, unrelated to chronic hypertension (except that chronic hypertension may predispose to it).

## Transient Hypertension

Also called gestational or late hypertension, transient hypertension is the diagnosis for mere rises in blood pressure without significant edema or proteinuria, with a return of the blood pressure to normal within 10 days after delivery. Followup studies by Berman,[16] Herrick and Tillman,[15] Chesley et al.,[130] Adams and MacGillivray,[17] and others indicate that transient hypertension usually recurs in later pregnancies and often predicts ultimate chronic hypertension. It probably most often is latent essential hypertension unmasked by pregnancy.

# Appendix

## Blood Pressure Measurement Protocol

Accurate and consistent blood pressure measurements are essential in order to establish a baseline and to monitor subtle changes throughout the duration of the pregnancy. Blood pressures should be taken in a standardized fashion by all personnel who see the pregnant woman during her antepartum, intrapartum, and postpartum care. In 1987, the American Heart Association (AHA) updated its standards for the fifth time since 1939 in its Recommendations for Human Blood Pressure Determination by Sphygmomanometers.[132] While this document primarily focuses on nonpregnant populations, many of its paradigms relate to the gestational period as well.

For accurate blood pressure measurements in all clinical situations, the AHA document recommends a standardized measurement technique. This includes:

- Having the patient sit* for 5 minutes prior to blood pressure measurement with the arm resting on a table at heart level (using the same arm on each measurement occasion for consistency)
- Measuring the bared arm for proper cuff size and having available commonly used cuff sizes for adults—notably regular and large adult cuffs with respective bladder widths of 12 cm and 15 cm (or in general, a bladder width of 40 percent of the arm circumference ensuring a bladder length which encircles 80 percent of the upper arm)
- Assessing for approximate systolic blood pressure level prior to measurement by finding where the radial pulse disappears with simultaneous palpation and inflation to disappearance
- Maintaining a slow, steady deflation rate of 2 to 3 mm Hg per second or per heartbeat when doing a reading
- Taking the average of the two readings (also recommended in JNC IV)[7] to help minimize variations in recorded blood pressure across time due to blood pressure's inherent variability (reflected in isolated readings)
- Using accurate equipment (mercury sphygmomanometer or calibrated aneroid).

It is important to remember that blood pressure measurements are influenced by the relationship of the cuff to the level of the heart (due to hydrostatic pressure, the effect of gravity on the column of blood). Blood pressure with the cuff higher than the level of the heart will be lower; blood pressure with the cuff lower than the level of the heart will be higher. For example, the practice of taking the blood pressure in the upper arm with the woman on her side will give falsely lower readings. Each centimeter above or below heart level translates to 0.8 mm Hg change. Thus these readings will naturally differ from those taken when the arm is appropriately at heart level (i.e., woman in supine position with the arm at her side or preferably seated with the arm resting on a standard table top).

* The World Health Organization (WHO) study group[10] notes that it probably does not matter whether the patients sits or lies slightly on the left side (15-30 degrees tilt), provided the same position is used. For practical purposes the seated position with the arm resting at heart level is the procedure used in virtually all prenatal clinics.

In listening to blood pressure readings, the first of at least two consecutive beats should be recorded as phase I, the systolic pressure. The AHA recommends that the onset of phase V (disappearance of sound), marked by the last sound heard, be used for defining diastolic pressure in adults. The onset of phase IV or muffling, sometimes used in the past, is harder to recognize and is subject to greater inter/intra observer variability. The vast body of epidemiologic evidence from clinical trials in nonpregnant populations, linking levels of diastolic pressure to increased cardiovascular disease risk, is based on the phase V criterion. In pregnancy phase V seems to correlate best with intra-arterial pressure.[33]

However, the AHA recognizes certain conditions in which phase V is absent, i.e., the Korotkoff sounds do not disappear but may be heard until the pressure in the cuff falls to near 0 mm Hg. Among these conditions are high cardiac output states including pregnancy. Also, the WHO has noted that in approximately 15 percent of pregnant women the diastolic pressure falls to zero before the last sound is heard. Under these conditions, phase IV is a better index of diastolic pressure than phase V. Both the AHA and WHO advise that if the phase IV (muffled) sounds are heard to zero (absent phase V), both phase IV and phase V readings should be recorded (e.g., 148/84/0 mm Hg). It seems prudent, given that the AHA recommends recording the onset of phase V as the diastolic blood pressure in adults, coupled with the probability of an absent phase V in a certain percentage of pregnant women in whom the onset of phase IV should then be recorded, that personnel should record both readings throughout the duration of the woman's pregnancy starting at the woman's initial prenatal visit. This will help to ensure that no information will be lost (e.g., baseline phase IV and V readings) and that subtle changes will be detected.

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NIH Publication No. 90-3029
August 1990